REMARKS

I. Introduction

Claims 1-3 and 11-26 are pending in this application. Claims 24-26 have been withdrawn by the Examiner as being drawn to a non-elected invention. Claims 4-10 have been cancelled according to a Preliminary Amendment filed on March 21, 2005.

According to the Office Action of February 20, 2008, the rejection of the pending claims under 35 U.S.C. § 103 is maintained. In response, Applicants submit this Request for Reconsideration. In view of the below remarks, Applicants respectfully request that the rejection be withdrawn.

II. Rejection Under 35 U.S.C. § 103(a)

Claims 1-3 and 11-23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang et al. (U.S. Pub. No. 2002/0049222) as evidenced by van Heek et al. (British Journal of Pharmacology, 2001, Vol. 134, pp. 409-417) in view of Somers (U.S. Pat. No. 6,147,250).

A. Previously asserted arguments

The present application is directed to a method of treating autoimmune disorders by administering to a patient suffering from such a disorder an effective amount of a sterol absorption inhibitor. In another embodiment, the present application is directed to a method of treating a patient suffering from an autoimmune disorder by administering, in addition to the sterol absorption inhibitor previously mentioned, a HMG-CoA reductase inhibitor. The formation of lipid rafts within the cell membranes of leukocytes play a critical role in T-cell and B-cell activation, antigen presentation, adhesion molecule function, and chemokine receptor signaling, each of which is associated with the pathogenesis of autoimmune disorders. Because both cholesterol and plant sterols are essential to the structure of these rafts, and thus the downstream autoimmune pathogenesis, Applicants have discovered that reducing the intestinal disruption of cholesterol and/or plant sterols can provide an effective method of treating or preventing autoimmune diseases by disrupting the formation of these lipid rafts.

Yang teaches a method of treating conditions associated with inflammation, including arthritis and multiple sclerosis, by administering modulators of chemokine receptor activity.

According to Yang, activation of the chemokine receptor CCR-2 by chemo-attractant protein-1 (MCP-1) plays a major role in monocyte recruitment to inflammatory sites, and opposition of this activity will sufficiently suppress the immune response to produce therapeutic benefits in immuno-inflammatory and autoimmune diseases. Yang, at ¶ 0006. Thus, Yang's invention is directed to compounds that, acting alone, can treat conditions associated with inflammation by modulating chemokine receptors such as the CCR-2 receptor. Yang, at ¶ 0007-0009. The compounds taught by Yang to accomplish this have at least two asymmetric centers at the 1- and 3-positions of the cyclopentyl ring and are of the general formula shown as in Yang at paragraphs [0010] through [0114].

Applicants, on the other hand, have discovered that certain sterol absorption inhibitors can, acting alone, treat and prevent autoimmune disorders by disrupting the formation of lipid rafts within the leukocytes. The compounds of Yang are structurally dissimilar to the compounds of Formulae I-IX used in the claimed methods of the present invention. The compounds recited by Applicants in Formulae I-IX are sterol absorption inhibitors, which do not inhibit activation of CCR-2 receptors, and Yang fails to disclose or suggest that such compounds could be used instead of CCR-2 modulators to treat a patient suffering from an autoimmune disorder.

Yang also discloses that his CCR-2 modulators can be co-administered with various other active ingredients which are not CCR-2 modulators, such as cholesterol absorption inhibitors like ezetimibe. Yang, at ¶ 0371. ***However, there is no indication in Yang that these other compounds are capable of treating or preventing an autoimmune disorder.*** The inclusion of such cholesterol absorption inhibitors in Yang is for other, more conventional uses of these compounds. At the time Yang filed his application it was unknown that ezetimibe could be used for treating or preventing autoimmune disorders. Thus, absent any indication to the contrary, co-administering ezetimibe with the CCR-2 receptor modulator in Yang was clearly intended to lower plasma cholesterol rather than to treat the autoimmune disorder itself. If in fact Yang had known of the propensity of sterol absorption inhibitors to treat autoimmune disorders, there would be no need to co-administer it with the primary compound taught in Yang. Further, there is no indication in any of the cited art that such a sterol absorption inhibitor would be successful

in treating an autoimmune disorder. It is a principal of patent law that, in making a rejection for obviousness under 35 U.S.C. § 103(a) there must be at least a reasonable expectation of success in modifying the cited art references. See *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); M.P.E.P. § 2143.02.

This deficiency of Yang is not cured by the disclosure of Van Heek or Somers. Van Heek is not directed to the treatment of autoimmune disorders at all but is instead concerned with the effect of ezetimibe in the treatment of atherosclerosis. Somers is directed to HMG-CoA reductase inhibitor compounds that are allegedly useful in lowering LDL levels and selectively inhibiting the expression of vascular cell adhesion molecule-1 (VCAM-1). According to Somers, HMG-CoA reductase inhibitors inhibit adhesion molecule functions in leukocytes. Somers is not directed to, nor does it disclose, the use of sterol absorption inhibitors, such as ezetimibe, or the use of these compounds in the treatment of autoimmune disorders.

Applicants have discovered that disrupting lipid raft formation in the plasma membrane of leukocytes will prevent the leukocyte trafficking which causes autoimmune disorders. The relationship between lipid raft formation and autoimmune disorders was not disclosed in Yang, which is focused instead on the relationship between the CCR-2 chemokine receptors and certain disorders, or Somers, which is directed to the relationship between cardiovascular disorders and the expression of VCAM-1. Further, the ability of sterol absorption inhibitors to treat autoimmune disorders or affect adhesion molecule function was also unknown. The cited art gives no reasonable expectation of Applicants' success since, as previously mentioned, the cited art is instead focused on the treatment of autoimmune disorders by mediating other biochemical pathways, namely the CCR-2 and VCAM-1 receptors. Consequently, one skilled in the art would not find it obvious in light of the cited art to administer a sterol absorption inhibitor, such as ezetimibe, to a patient to treat an autoimmune disorder.

B. Response to new arguments asserted in the Office Action of February 20, 2008.

In order for the Patent Office to meet its burden, it must establish that combining the references teach, suggest or motivate a skilled artisan to administer a sterol absorption inhibitor to treat an autoimmune disorder because the references establish that sterol absorption inhibitors disrupt lipid raft formation in leukocytes. The Office Action does not meet this burden.

On page 4, the Office Action acknowledges that Yang does "not teach sterol absorption inhibitors that disrupt lipid raft formation of leukocytes." Somers does not overcome this deficiency because Somers likewise does not teach disrupting lipid raft formation. Instead, Somers is directed to inhibiting VCAM-1, which does not relate in anyway to disrupting lipid raft formation, and therefore fails to teach, suggest or motivate a skilled artisan to employ such a strategy to treat an autoimmune disorder. The recited sterol absorption inhibitors are not HMG-CoA inhibitors, and do not inhibit VCAM-1. They act via a completely different mechanism making it unpredictable, and consequently not obvious, to use the recited sterol absorption inhibitors to treat an autoimmune disorder.

On page 6, the Office Action contends that Somers's HMG-CoA reductase inhibitor provides motivation for a skilled artisan to use a sterol absorption inhibitor, without explaining why the skilled artisan would believe that the sterol absorption inhibitor would disrupt a lipid raft formation. Without such an explanation, the Office Action does not establish a *prima facie* case for obviousness.

According to the Board of Patent Appeals and Interferences, the Patent Office must provide some reason, suggestion or motivation to inhibit the specific pathway of sterol absorption inhibitors. *See In re June*, App No. 08/245,282, 2004 WL 77414 (BPAI 2004). In *June*, the examiner argued "that 'Vandenberghe teaches that herbimycin A inhibits a protein tyrosine kinase and one of skill would expect that inhibition of protein kinase would affect the PI 3-kinase and ultimately the D3 phosphoinositide production.'" 2004 WL 77414 at *9. The Board held that

> [a]t best, the statement of the rejection establishes that individual parts of the claimed invention were known in the prior art. Okada describe the role of PI3K in insulin induced glucose transport and antilipolisis in rat adipocytes but does not address T-cell activation. Ward 1993 would appear to suggest that activation of PI3K and subsequent D-3 lipid metabolism may be important signaling events in CD-28 mediated co-stimulation and T-cell activation following ligation by B7, but provides ***no reason, suggestion or motivation to inhibit such a metabolic pathway.***

(Emphasis added). *Id.* at 9. Thus, references like Somers that are directed to HMG-CoA reductase inhibitors that lower LDL levels are immaterial to whether there is any motivation to

disrupt lipid raft formation with sterol absorption inhibitors because sterol absorption inhibitors and HMG-CoA reductase inhibitors act on different pathways. HMG-CoA reductase inhibitors inhibit HMG-CoA reductase, which is a rate controlling enzyme of the mevalonate pathway, the metabolic pathway that produces cholesterol and other isoprenoids; while sterol absorption inhibitors reduce the intestinal disruption of cholesterol and/or plant sterols.

Since the Office Action does not provide any reason to use a sterol absorption inhibitor instead of a HMG-CoA reductase inhibitor; it does not state any motivation to combine the references in a manner that would result in the recited invention. Without such motivation, the Office Action does not establish a *prima facie* case of obviousness.

IV. Conclusion

For all of the foregoing reasons, Applicants submit that pending claims 1-3 and 11-26 are patentable over the cited references, and are in condition for allowance. Accordingly, reconsideration of the rejections and allowance of pending claims 1-3 and 11-26 are respectfully requested.

Should the Examiner have any questions regarding any of the foregoing or wish to discuss this application in further detail to advance prosecution, the Examiner is invited to contact Applicants' undersigned representative at the telephone number provided below.

Respectfully submitted,

By _____

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